

## The gut microbiome and mental health: Taking baby steps

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To say that the gut microbiome is a hot topic, both in the scientific community and popular press, is an understatement. Per PubMed, the number of articles that include “gut microbiome” or “gut microbiota” in the title showed exponential growth over the past decade, with only 37 articles in 2008 and 1537 in 2018 (Fig. 1). Incredibly, this is over a 4000% increase. Expansion of research in this area shows no signs of stopping.

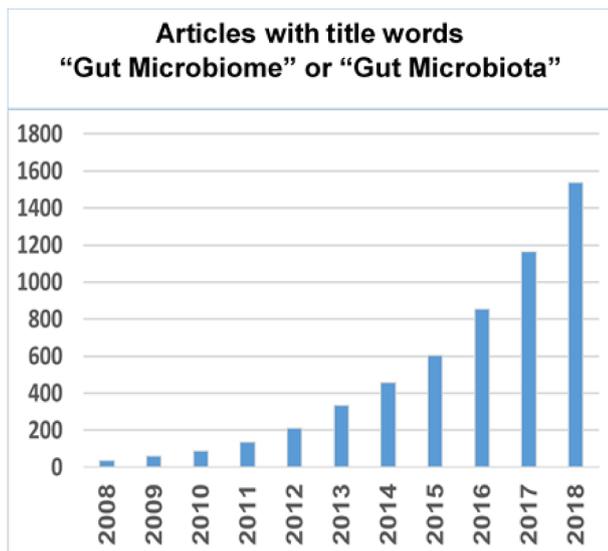


Fig. 1. The total number of articles per year that include the words “gut microbiome” or “gut microbiota” per PubMed.

A key topic underlying this explosion has been the gut microbiome and mental health. Not only are articles on this topic prolific, but they are also increasing in both sophistication and impact. In fact, the first two awards for the newly established Brain, Behavior, and Immunity Impact Award, which recognizes the author of the paper with the most citations among articles published 3–4 years prior, have both gone to articles with a focus on the link between the gut microbiome and mental health. Demonstrating the wide ranging clinical relevance and

design approaches, the first article by de Theije and colleagues focused on a murine model of autism spectrum disorders (de Theije et al., 2014), while the second by Jiang and colleagues examined the fecal microbiota in adults with major depressive disorder (Jiang et al., 2015).

While interest in this area is very well justified, “baby steps” will be helpful to advance the literature on the gut microbiome and mental health in two ways. First, studies on early life, in both infants and fetal development, are critical. The current article by Aatsinki and colleagues contributes in important ways to this rapidly expanding literature (Aatsinki et al., 2019). This study reports that, among a cohort of 301 infants followed longitudinally, gut microbiome composition measured at only 2.5 months of age was related to temperament at 6 months of age, with modifying effects based on infant sex. What is the relevance of temperament for mental health? Temperament reflects both affective-motivational and attentional style and is a key construct for assessing behavior in early life. Critically, temperament in early childhood have predictive value for personality, behavior, and risk for psychopathology in later childhood, adolescence, and adulthood (Rothbart and Posner, 2006). As appreciated by readers of BBI, psychiatric disorders account for a larger portion of disability in developed countries than any other group of illnesses including cancer and heart disease (Reeves et al., 2011). Thus, by providing an early window into psychological functioning, the current data from Aatsinki and colleagues have relevance for understanding long-term risk for psychopathology throughout the lifespan.

The current study parallels prior data from our group which show associations between temperament and gut microbiome composition in toddlers at approximately 24 months of age, also in a sex-dependent manner (Christian et al., 2015). By demonstrating that these types of associations are present even in the first few months of life, the findings from Aatsinki and colleagues highlight the potential promise of early life intervention during a period when the gut microbiome may be particularly malleable to change. In fact, emerging evidence also highlights the potential importance of the maternal microbiome and fetal development in the relationship between the gut microbiome and mental health (Gur et al., 2017).

“Baby steps” are also needed in another sense; a careful and rigorous approach will best advance the move toward clinical application. Research on the gut microbiome and mental health/behavior is predominately preclinical (i.e., animals models) and/or correlational in

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design. To make the leap to clinical translation, there remains a critical need for data on the causal direction of these observed associations, as well as the ability to manipulate the microbiome in a beneficial manner. Indeed, while making an important contribution to the literature, the article by Aatsinki and colleagues does not provide evidence regarding causal direction of the observed effects. As Dinan & Cryan commented in their recent BBI Viewpoint article, despite enormous progress in this area, the studies needed to directly impact patient care are yet to be conducted (Dinan and Cryan, 2019).

Although the work needed to inform interventions is not yet mature, the rapid expansion of science on the gut microbiome has been reflected by an explosion in coverage (of varying quality and veracity) in the popular press. The proliferation of advice and products is remarkable. Appropriately, outlets ranging from peer-reviewed review articles to social media warn of the perils of the “hype” and “mayhem” in relation to the gut microbiome (Bik, 2016; Senapathy, 2016). For example, a well-titled blog post on Forbes, “Keep Calm and Avoid the Microbiome Mayhem,” targeting a lay audience wisely advises careful consumption of current interventional claims with regard to the gut microbiome, with an eye towards separating the “credible microbiome wheat from the evidence-sparse chaff” (Senapathy, 2016). Ultimately, given the variety of health conditions, ranging from obesity, allergy, and mental health in which the gut microbiome is implicated, the likelihood of unanticipated secondary effects is great and such efforts should be approached thoroughly and with care – i.e., with “baby steps”.

In sum, as an area of investigation, the gut microbiome and mental health is rapidly expanding. The current article contributes to this growing literature in a novel and important way by demonstrating associations between the gut and temperament in very early life in humans, contributing to a limited clinical literature in this area while also focusing on a critical developmental timeframe. These and other emerging data hold great promise for improving human health. As

evidenced by prolific coverage of this topic in the popular press, the public is listening, and industry is eager to capitalize. The scientific community can help to shape this narrative through responsible and clear communication and excellent study design. As the microbiome story unfolds, the truth will be whittled from the noise and hype – with potentially enormous effects on human health.

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